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EXAMINER	
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ART UNIT	PAPER NUMBER
1812	10

DATE MAILED: 02/09/95

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

a) ☒ is extended to run 6 mos. or continues to run _____ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 2/3/95 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☒ will be entered ☐ will not be entered and the status of the claims will be as follows:

   Claims allowed: None
   Claims objected to: _____
   Claims rejected: 30-35, 38-43

   However;

   ☒ Applicant's response has overcome the following ~~o~~ rejection(s): improper dependency of Claims 39-43, Rejection of 31+39 under §101.

4. ☒ The ~~affidavit, exhibit~~ or request for reconsideration has been considered but does not overcome the rejection because Please See Attached.

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☐ Other

See attachment

PTOL-303 (REV. 5-89)

Part III: Detailed Office Action

Claims 36 and 37 have been cancelled. Claims 32, 33, 40 and 41 have been amended. Claims 30-35 and 38-41 are under consideration.

Claims 39-43 are objected to as being improperly dependent upon cancelled claims 36 and 37.

All previous rejections under 35 U.S.C. §112, second paragraph are withdrawn in view of applicants' amendments.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to make an enabling disclosure, and Claims 31 and 39 are rejected under 35 U.S.C. §101. The current specification provides enablement only of the production of the peptides of the invention and their use in vitro. No evidence of in vivo utility is presented, nor has the applicability of the in vitro test results to the use of the claimed protein in vivo been established. It is submitted that there is sufficient reason to doubt that applicant's invention has utility in vivo. The ability to inhibit binding and infection of CD4+ cells by HIV in culture is insufficient to establish a practical utility for applicant's invention as claimed. It is clear from the specification as filed as well as the claims

Drop 101 maintain 112

themselves that applicant intends the invention to be used as a therapeutic, administered to patients as an antiviral. The skilled artisan would not accept the inhibitory effect seen in cells in vitro as being predictive or correlative of an in vivo function for applicant's invention. Consequently, applicant's invention lacks patentable utility, and the specification as filed fails to teach how to use the claimed invention.

Applicant's invention remains nothing more than an inhibitory phenomenon observed in cells in culture. This is a springboard for further research, but is insufficient to establish a practical utility for the invention. The skilled artisan, as well as the current state of the art, would not accept that such observations are correlative or predictive of in vivo delivery and efficacy of such proteins as therapeutics.

The Examiner notes Applicants traversal that submission of *in vivo* data cannot be required. Applicants are not required to present any specified data, including *in vivo* data. Applicants are, however, required to provide evidence acceptable to one skilled in the art which establishes the truth of the statement of utility and enablement at the time the application was filed.

Finally, applicant is directed to note Ex parte Balzarini 21 USPQ2d, 1892 at page 1892 (Bd. Pat. App. and Int. 1991):

> Holding that results of applicants' in vitro tests do not establish utility of claimed pharmaceutical compounds for in vivo treatment of AIDS in humans does not equate to holding that human clinical testing is only acceptable proof of utility, but rather reflects conclusion that applicants have failed to rebut examiner's showing that those skilled in art would not associate successful in vitro results with successful in vivo treatment; neither issuance of other patents for treatment of AIDS in humans, in which no evidence of in vivo testing was submitted, nor moderate success of other compounds in treating AIDS, requires contrary result on utility issue, since allowance of similar claims to others has long been held immaterial, and since applicants have submitted no evidence that two compounds of subject application are considered so structurally similar to successful compounds that similar properties would be expected.

Further, on page 1897 it is found:

> We do not presume to tell appellants what evidence would be acceptable in rebuttal of these rejections. While we are not requiring human clinical trials, it may well be that in 1987 or even now those skilled in this art would not accept anything short of such human clinical trials. There is no evidence of record that experimental animal models have been developed in this area which would be predictive of human efficacy.

Enablement of the current specification as filed is not commensurate in scope with claims to CD4-Ig chimeric proteins linked to toxins of any sort, for reasons cited in the previous Office Action at the paragraph bridging pages 2-3. Applicants seem to have misread the original objection, as careful examination of such reveals that the Examiner was making the point that, as now admitted by applicants, toxins are not useful as diagnostic reagents. Applicants arguments that the claimed toxins are enabled are not found persuasive for reasons cited above.

Claims 31-33, and 39-41 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 30-35 and 38-43 are rejected under 35 U.S.C. §103 as obvious over U.S. Patent Number 5,116,964 either alone or taken with applicants admissions in the specification of the state of the prior art for reasons of record in the previous Office Action at pages 4-5. Applicants' argument that the '964 patent teaches away from the claimed invention at column 7 has been fully considered but is not deemed persuasive. The cited portion of the patent is directed to a specific limitation of the claimed invention, which limitation was included to avoid the prior art. Upon examination of the patent as a whole, one finds multiple teachings toward the currently claimed invention, for example at Column 5, lines 1-5 and 48-55, and Col. 30, lines 54-66. Thus, in summary, the Capon patent taken as a whole teaches strongly *toward* the use of CD4-Ig chimeras for the purpose of targeting HIV infected cells.

Claims 30-35 and 38-43 are rejected under 35 U.S.C. § 103 as being unpatentable over WO89/02922 in view of Capon et al. (Nature) for reasons cited in the previous Office Action at pages 5-6. Applicants argument that neither cited reference teaches the inclusion of the entire hinge domain of the IgG2 moiety is not persuasive. The '922 publication clearly discloses the use of the *entire* Ig constant region, for example at page 13 in the discussion of an IgG1 adheson. The ordinary artisan is well aware that the *entire* constant region of an immunoglobulin comprises the entire hinge domain as well as the "remaining" (carboxyl terminus) portion of the molecule. The '922 publication also clearly teaches the use of IgG2, as cited in the previous Office Action:

> " The first paragraph, p. 13 states suitable fusion partners to include IgG-1, -2, -3 or -4, IgA, IgE, IgD, or IgM. The paragraph bridging pp. 15-16 discloses fusions which further comprise an adheson conjugated with a toxin. Pharmaceutical

compositions are disclosed at p.27,§1. "

The advantages of using IgG2 pointed out by applicants in their traversal of the rejection are properties which were known to be associated with IgG2 prior to the current invention; therefore, the claimed invention merely uses the suggestions of the prior art to make an obvious combination for its known and expected properties. Applicants argument that the cited references do not teach conjugation with a toxin are not persuasive in view of the quotation from the previous Office Action, above; the reference clearly and directly suggests conjugation to a toxin.

No claims are allowed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed to Lorraine Spector, Ph.D. at telephone number (703) 308-1793.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the

Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The CM1 Fax Center number is (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

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Serial Number 07/960,440
Art Unit 1812

Attachment to Advisory Action, Paper Number 10:

The rejection of claims 31 and 39 under 35 U.S.C. §101 is withdrawn.

Applicant's arguments filed 2/3/95 have been fully considered but they are not deemed to be persuasive.

The objection to the specification and rejection of claims 31-33 and 39-41 under 35 U.S.C. §112, first paragraph is maintained for reasons of record. Applicants arguments have been fully considered but are not persuasive for reasons of record. With regard to the issue of toxin conjugates, applicants still appear to misunderstand the Examiner's position; the objection is not on the basis that one of skill in the art would not be able to *make* the claimed matter, but rather that the current specification as filed does not teach *how to use* the invention as it is claimed, for reasons of record.

With regard to the rejections under 35 U.S.C. §103, it is noted that the portions of the patent were cited to demonstrate disclosure of CD4/Ig chimeras. The fact that the specifically cited constructions were bispecific and/or bifunctional does not teach against the current invention; the cited references must be viewed for their teachings as a whole, and in the combination cited. With respect to the '922 publication, applicants argument is not persuasive because deletion of the CH1 domain does not impart patentable distinction to the construct, especially in view of Capon, which specifically teaches using an Fc fragment, which fragment would not contain CH1.

GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800

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